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COMPLETE SPECIFICATION

Readily Soluble Dry Preparations of Swelling Substances

We, FARBENFABRIKEN BAYER, a German Company recognised under German Law, of (22c) Leverkusen-Bayerwerk, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention comprises readily soluble dry preparations of swelling substances and a process of producing such preparations, the process involving the subjection of aqueous solutions of swelling substances to freeze-drying which comprises the removal of water from frozen solutions of solid substances by sublimation of ice at low pressure.

It is known that by subjecting aqueous solutions of solid substances to freeze-drying the substances are obtained in the form of a porous skeleton which, due to its rapid wetting ability allows an almost instant redissolution of the dry substances. However, experience has shown that a skeleton of solid substances which tend to swell in solvents and to yield viscous solutions does not show this effect. The skeleton of such substances when contacted with solvents forms clots of various sizes which dissolve very slowly or not at all. This phenomenon is due to the fact that the particles of the porous skeleton remaining after freeze-drying, which are first contacted with the solvent, pass immediately into the swollen state and agglutinate, thus preventing the wetting of the particles being beyond the agglutinated layer.

According to the present invention swelling substances tending to agglutinate on contact with a solvent, e.g. water, are converted by freeze-drying into a readily soluble skeleton form, by adding a crystallizable substance, readily soluble in water, to the viscous solution of the swelling substance before the solution is subjected to freeze-drying. In this process the individual particles of the substance tending to agglutinate are surrounded on freeze-drying with a thin layer of the added crystallizable substance. On redissolution of the dry preparation obtained after freeze-drying, the said layer prevents the agglutination of the swelling substance until the solvent has contacted all particles of the preparation.

The nature of the soluble agent added according to the invention depends on the intended use of the preparations. It may be a sugar, a salt, citric acid, urea or one or other of various crystallizable substances of organic or inorganic nature, or a mixture of such substances. The amount of the added agent depends on the nature and the agglutinating tendency of the colloidal substances, which may be of natural or synthetic origin, as well as on the nature of the agent itself. Simple tests will readily determine the optimum amount of the addition for preventing the agglutination of the swelling substance.

The invention is especially useful in the production of dry preparations for foods and medicines which contain swelling substances and which are intended to be dissolved immediately prior to their administration, for instance, combinations of vitamins or hormones and polyvinyl pyrrolidone. The addition of sugar-like agents, for instance sucrose, glucose or sorbite, to preparations to be used for parenteral application, have proved to be especially suitable since these agents are well compatible and their solutions exert only a low osmotic pressure; they may therefor be applied in comparatively high concentrations without yielding hypertonic solutions on redissolving the dry preparations.

The following examples are given to illustrate the invention the percentages mentioned being by weight:—

EXAMPLE 1:

An aqueous gelatine solution of 2½% strength is mixed with 4% sucrose calculated on the weight of the solution and subjected to freeze-drying. The remaining porous, white, dry mass is completely dissolved immediately on adding water.

EXAMPLE 2:

An aqueous gelatine solution of 2½% strength is mixed with 5% sodium chloride calculated on the weight of the solution and subsequently subjected to freeze-drying. A white, porous mass remains which can very easily be redissolved in water.

When a gelatine solution of 2½% strength is subjected to freeze-drying without the addition of the agents employed in Example 1 or 2, a dry preparation is obtained which cannot completely be redissolved in water, even within some hours, due to agglutination.

EXAMPLE 3:

An aqueous solution containing per 100 ml. the therapeutically required amount of a physiologically active ingredient, which is unstable in an aqueous solution —e.g. 25,000 international units of the hormone of the anterior pituitary gland— and 2.5 grams of polyvinyl pyrrolidone per 100 ml., is mixed with 4.5 grams of sucrose per 100 ml. After dissolution of the sucrose, ampoules are filled under sterile conditions, each with 2.6 ml. of the solution, and subjected to freeze-drying. The ampoules are then closed by melting their tops. The dry preparation remaining in each ampoule yields a clear viscous solution within one minute when 1.3 ml. of sterilized water are added. The solution may be used directly for injection and exhibits the full activity of the starting material. A dry preparation produced without the addition of sugar, however, under otherwise equal conditions, gives no clear solution when an equal amount of water is added.

EXAMPLE 4:

5:00 ml. of an aqueous solution containing 100,000 units of the circulatory hormone callicrein and 90 grams of sucrose are added through a sterilized filter to a sterilized solution of 50 grams of polyvinyl pyrrolidone (k-value 90); see Fikentscher, "Cellulosecchemie," 1932, p. 58) in 500 ml. of distilled water. The viscous phase is thoroughly mixed with the aqueous phase until a uniform solution is obtained.

The solution is then filled into wide-necked ampoules of 5 ml. under sterile conditions in quantities of 1.5 ml., cooled to −40° C. and subjected to freeze-drying. The ampoules are then closed. On adding 5 ml. of distilled water to the dry preparation contained in each ampoule a clear solution is obtained within one to three minutes, which contains 150 units of callicrein that owing to its combination with polyvinyl pyrrolidone exhibits a protracted activity.

What we claim is:—

1. Process for the preparation of readily soluble dry preparations of swelling substances tending to agglutinate upon the addition of water, which comprises adding to an aqueous solution of the swelling substance a crystallizable readily water-soluble substance such as a sugar, a salt, citric or urea, and subjecting the solution to freeze-drying.

2. Process according to claim 1 wherein the solution to be subjected to freeze-drying contains, besides the swelling substance and the soluble crystallizable substance, a therapeutically active substance.

3. Process according to cliams 1 and 2 wherein the solutions subjected to freeze-drying contains callicrein, polyvinyl pyrrolidone and a water-soluble crystallizable substance, such as sucrose.

4. Process for the preparation of readily soluble, dry preparations, substantially as described in any of the foregoing Examples.

5. Readily soluble, dry preparations of swelling substances prepared as claimed in any of the preceding claims.

CARPMAELS & RANSFORD.
Agents for Applicants,
24, Southampton Buildings,
Chancery Lane, London, W.C.2.

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